On the Mechanisms of Ventricular Tachycardia Acceleration During Programmed Electrical Stimulation

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Background. The pathophysiological mechanisms leading to acceleration of ventricular tachycardia (VT) are still unclear.

Methods and Results. High-resolution epicardial mapping was used to study the mechanisms of VT acceleration by programmed electrical stimulation (PES) in a model of sustained reentrant VT in Langendorff-perfused rabbit hearts (n=40). Three different mechanisms responsible for acceleration of VT were identified: 1) induction of double-wave reentry (n=6), defined as the occurrence of two successive activation waves circulating in the same direction in the same circuit; 2) change to a functionally determined circuit (n=4), defined as reentry of the impulse around a functional line of block without involvement of a fixed obstacle; and 3) change of the reentrant circuit to reentry within a different, faster anatomic pathway (n=3). Analysis of 81 episodes of sustained monomorphic VT induced by PES in 74 patients with clinically documented sustained VT in the setting of chronic coronary artery disease showed that in 22 episodes VT was suddenly accelerated by PES (mean cycle length, from 345±73 to 277±71 msec, p<0.01).

Conclusions. With the observations made in the experimental model, the following tentative classification of the mechanisms of VT acceleration of the 22 episodes was made: 1) induction of double-wave reentry in two, 2) change to a functionally determined circuit in four, and 3) change to reentry within a faster anatomic circuit in 16. Simple criteria suggest that these mechanisms may apply in the clinical situation. (Circulation 1991;83:1621–1629)

Since the introduction of the technique of programmed electrical stimulation (PES) of the heart, important information has been obtained about the pathophysiological mechanisms of cardiac arrhythmias in humans.\(^1\) The mechanisms of initiation and termination of ventricular tachycardia (VT) by PES have been the subject of extensive investigations.\(^2\)–\(^6\) These studies have shown that VT can not only be terminated but also accelerated by PES.\(^5\)–\(^6\) Acceleration of VT during PES has been observed in about one third of the cases.\(^5\) Despite this high incidence of acceleration of VT by pacing, limited information is available concerning the pathophysiological mechanisms of acceleration because detailed mapping of electrical activation during VT acceleration can only rarely be obtained.\(^7\)–\(^8\) The purpose of this study was to investigate the mechanisms of acceleration of reentrant VT by PES in an animal model of reentrant VT. High-resolution mapping was used to assess the mechanisms of acceleration of VT. Based on this experimental study, criteria were developed in an attempt to classify the underlying mechanisms of VT acceleration in humans.

Methods

Experimental Studies

In the first part of the study, a previously reported experimental model of reentrant VT around a fixed obstacle in two-dimensional, uniform, anisotropic epicardial tissue of Langendorff-perfused rabbit hearts was used.\(^9\)–\(^10\) Forty Flemish rabbits of both sexes weighing between 3.4 and 4.4 kg were used. In 35 hearts, a single anatomic obstacle was created in the two-dimensional layer of epicardium by applying a cryoprobe at a 10-mm distance parallel to the left
antior descending coronary artery (LAD). This procedure produced an area of about 25 x 10 mm where the surviving epicardial layer was destroyed. Thus, the final preparation in these 35 experiments consisted of a perfused epicardial ring in the free wall of the left ventricle (Figure 1, left panel). In five other hearts, two anatomic obstacles were created by a smaller epicardial cryoprobe applied at two locations at a distance of 10 mm from the LAD. This procedure produced two areas of about 10 x 6 mm of destroyed epidermis with surviving epicardium around and between the two obstacles. Thus, the final preparation in these five experiments consisted of a figure-eight pattern of perfused epicardium in the free wall of the left ventricle (Figure 1, right panel).

Recording and stimulation. High-resolution mapping of epicardial excitation was performed with a spoon-shaped electrode containing 256 individual electrodes at regular distances of 2.25 mm. With this mapping electrode, 256 unipolar electrograms were recorded simultaneously from the left ventricular epicardium. The 256-channel mapping system was used for acquisition, storage, and data analysis has been described. Three bipolar reference electrodes were positioned around the obstacle at the apex, the base, and the free wall of the left ventricle. PES was performed with a programmable constant-current stimulator delivering square pulses of 2 msec in duration at twice diastolic threshold for regular stimulation and at four times diastolic threshold for the induction of premature beats. Bipolar stimulation could be performed through each one of the three reference electrodes. Reentrant VT was induced by one to three early extrastimuli applied after a 10-beat drive at a cycle length of 250 msec or by means of short bursts of rapid pacing. During the VT, one to three early premature stimuli and trains of five to 10 stimuli were given. Burst pacing was started with a cycle length of 150 msec and was subsequently shortened in steps of 10 msec until capture of the ventricle failed. Acceleration of VT by PES was studied by stimulation at each of the three reference electrodes.

Clinical Studies

In the second part of this study, 81 different episodes of sustained monomorphic VT were retrospectively studied. These 81 VTs were induced in 74 patients (68 men and six women) with a mean age of 56.2 ± 12 years and who had spontaneous sustained VT in the setting of chronic coronary artery disease. All studies were performed in the absence of antiarrhythmic medication. During all episodes of induced VT, one, two, or three extrastimuli or trains of 10 stimuli at rates faster than the VT were introduced at the right ventricular apex. The end point of the pacing protocol was termination of VT, acceleration of VT (defined as a decrease in cycle length by more than 10%), or induction of a poorly tolerated ventricular arrhythmia requiring termination by direct-current shock. During 48 episodes of VT, the ventricular effective refractory period could be measured. In the remaining 33 episodes, the refractory period could not be determined because the arrhythmia was poorly tolerated or because a single premature beat induced acceleration, termination, or change of the VT. The ventricular effective refractory period was measured by introducing single premature beats at the right ventricular apex during VT starting late in diastole with increasing degrees of prematurity. The advancement of the first beat of the VT after the stimulus indicated capture and resetting of the circuit. The premature beat was then decreased by 10-msec intervals until ventricular capture failed. The longest interval (measured from the beginning of the QRS complex to the stimulus) not capturing the circuit was considered to be the effective refractory period at the site of stimulation during VT. The excitable period during VT was estimated by the difference between the cycle length of the VT and the coupling interval of the earliest possible premature beat that could reset the VT.

Results

Experimental Studies: One Obstacle

Electrophysiological characteristics of VT. In all 35 experiments with a single obstacle, PES induced sustained regular VT. Epicardial mapping showed that the mechanism of VT was reentrant excitation around the obstacle in all cases. The cycle length of VT ranged from 124 to 215 msec (mean, 156 ± 14 msec). The cycle length of the VT varied because of differences in the size of the obstacle and variations in the average conduction velocity around the obstacle. As previously reported, initiation of VT occurred when a premature stimulus was blocked in one direction around the obstacle and traveled slowly enough in the opposite direction to reexcite the area.
proximal to the block. Spontaneous termination of VT was never observed. However, rapid pacing could terminate all episodes of VT.

**Acceleration of VT by PES.** In 10 experiments, PES induced sudden acceleration of VT. Epicardial mapping disclosed two different mechanisms responsible for VT acceleration: 1) double-wave reentry and 2) change to a functionally determined circuit.

In six experiments, double-wave reentry was induced. During this phenomenon, which was recently described in detail,\textsuperscript{10} two successive waves circulate simultaneously in the same direction around the same circuit. The most important characteristics of double-wave reentry are 1) it can only be induced during VT with a large excitable gap, and 2) the cycle length of VT after acceleration depends on the cycle length of VT before acceleration. On average, the cycle length of double-wave reentry was 56±6% of the cycle length during single-wave reentry. In all cases, the cycle length of double-wave reentry was less than 70% of the cycle length of the single-wave VT.

In four experiments, PES accelerated VT because of induction of a functionally determined circuit with a shorter revolution time. These functional circuits have been described\textsuperscript{9,12} and represent reentrant activation without the involvement of a fixed anatomic obstacle. In Figure 2, an example of acceleration of VT by induction of a functional circuit is shown. During sustained monomorphic VT with a cycle length of 144 msec, the application of 12 stimuli with a cycle length of 80 msec changed the morphology of the electrograms and shortened the cycle length of the VT to 108 msec. The two panels represent the activation maps during the VT before (left panel) and after (right panel) acceleration. During the slow VT, the excitation wave propagated in a clockwise direction around the obstacle, activating each point of the circuit at regular 144-msec intervals. Conduction velocity was high in the base and in the free wall of the left ventricle where the impulse propagated parallel to the epicardial fiber orientation. In the narrow “corridor” between the LAD and the obstacle, propagation occurred transverse to the fiber axis at a considerably slower speed (anisotropy). After acceleration of the VT, the activation map demonstrated a functional circuit with a cycle length of 108 msec. The functional nature of this circuit is apparent from the absence of conduction block in that area during the slower VT before acceleration. From the functional reentrant circuit, the impulse propagated both clockwise and counterclockwise around the fixed obstacle to collide at 82 msec at the opposite side of the obstacle. The characteristics of acceleration by change to a functional circuit are 1) the accelerated VT is regular, sustained, and has a cycle length independent of the cycle length before acceleration (in the four experiments, VT accelerated from a mean cycle length of 163±28 to 118±9 msec), and 2) the cycle length of the accelerated VT was only slightly longer (<30 msec) than the effective ventricular refractory period during VT (mean, 109±8 msec).

**Experimental Studies: Two Obstacles**

**Electrophysiological characteristics of VT.** In the five experiments with two obstacles, PES induced reentrant VT around one of the obstacles in all experiments. Depending on the size of the circuit, the cycle length of VT ranged from 125 to 164 msec (mean, 146±14 msec). As in the experiments with a single obstacle, induction of VT occurred when the impulse was blocked in one direction around one of the obstacles and when conduction in the opposite direction was slow enough to reexcite the area proximal to the block.

**Acceleration of VT by PES.** In three of the five experiments, PES induced acceleration of VT. The cycle length decreased from 153±13 msec before acceleration to 118±16 msec after acceleration. In this series of experiments, acceleration was caused by a change from the original anatomic circuit to another, faster anatomic reentrant pathway. With two obstacles present, premature stimulation or burst pacing terminated the first VT but simultaneously initiated a new VT around the other obstacle. Figures 3 and 4 illustrate this phenomenon. In the example shown in Figure 3, acceleration was induced by a series of eight stimuli (the first stimulus not capturing the ventricle) with a coupling interval of 90 msec. This converted the original VT with a cycle length of 135 msec into a VT with a cycle length of 98 msec. The maps of the two VT show that during the “slow” VT (left) the impulse rotated clockwise around the upper obstacle. The lower obstacle was not operative as a substrate for circus movement. Instead, the tissue around the lower obstacle was activated by two opposed wavefronts (one propagating clockwise and the other counterclockwise), which collided at 29 msec (double bars). After acceleration, the situation was completely reversed. As can be seen from the map of the “fast” VT (right), the VT was now caused by counterclockwise circus movement around the lower obstacle. The original circuit around the upper obstacle was interrupted and was activated by two opposed wavefronts colliding at the base at 86 msec (double bars). In Figure 4, an example from another experiment is shown in which a VT with a cycle length of 159 msec was accelerated by a single premature stimulus with a coupling interval at the site of pacing of 100 msec to a VT with a cycle length of 138 msec. In this case, during the original VT, the impulse rotated counterclockwise around the upper obstacle (left). The accelerated VT was caused by clockwise circus movement of the impulse around the lower obstacle (right). During both VTs, the obstacle that was not used for a reentrant pathway was circumvented by two opposite colliding wavefronts.
**Clinical Studies**

During the electrophysiological study in 74 patients, 81 episodes of different sustained monomorphic VT were induced by PES. The cycle length of the induced VT ranged from 255 to 560 msec (mean, 348±78 msec). The excitable gap (mean, 121±53 msec) and the ventricular effective refractory period during VT (mean, 226±21 msec) could be measured during 48 episodes of VT. Of the 81 episodes of VT, 24 were accelerated by PES. The ventricular rhythm directly after acceleration was sustained monomorphic VT in 22 episodes and was ventricular fibrillation in two episodes. The cycle length of the 22 episodes in which acceleration did not result in immediate ventricular fibrillation decreased from 345±73 to 277±71 msec. We analyzed the morphology of the QRS complex in the 12-lead electrocardiogram before and after acceleration. In eight episodes, the QRS complex morphology was similar in all 12 electrocardiographic leads (Figure 5). In 14 episodes, the morphology of the VT was different before and after acceleration. No significant relation was found between the number of extrastimuli necessary to induce acceleration and the cycle length of the VT before and after acceleration or the excitable gap or the ventricular refractory period during VT.

**Discussion**

There is substantial evidence that reentry is the most likely mechanism of VT occurring during the chronic phase of myocardial infarction.\(^8\),\(^13\),\(^14\) The criteria to demonstrate this mechanism during clinical electrophysiological study include the reproducible initiation and termination of VT by PES and the ability to entrain the VT.\(^14\) Direct proof of a reentrant circuit during VT has been obtained only in a few cases by extensive intraoperative mapping.\(^8\),\(^13\) Surgical treatment of these VT has been successful presumably because of interruption of the reentrant pathway.\(^15\),\(^16\) In our simplified experimental model of VT, high-resolution mapping allowed careful analysis of the events occurring during acceleration of the VT by PES. In the experiments with a single obstacle, we observed two different mechanisms of acceleration of the VT by PES. The first mechanism was the occurrence of double-wave reentry.\(^10\) This phenomenon
Results from penetration of a second impulse in the reentrant circuit that starts to propagate in the same direction as the original circulating wave. An excitable gap large enough to allow the second wave to fit into the circuit was a necessary condition for double-wave reentry to occur. Theoretically, the rate of the accelerated VT should be up to twice the rate of the original VT. However, we found that the actual cycle length of the accelerated VT was between 70% and 55% of the initial VT because of rate-dependent depression of conduction velocity. The second mechanism of acceleration of VT was the induction of a functionally determined circuit. As we previously demonstrated, in the absence of a central anatomic obstacle, the impulse may circulate around a line of functional block and the revolution time is mainly determined by the functional refractory period of the ventricle. Because of the anisotropic nature of the ventricular myocardium, a short excitable gap of 20–30 msec was present in these functional circuits. This short excitable gap is created by a low safety factor for conduction at the two pivoting points of the anisotropic circuit. In the experiments with two anatomic obstacles, a third mechanism of acceleration of VT by PES was observed. In this situation, introduction of one stimulus or a series of stimuli could terminate the original circuit and at the same time start reentry in another anatomic circuit with a shorter revolution time. Multiple potential circuits have been demonstrated in the canine postinfarction heart. El-Sherif et al showed that a train of stimuli can not only terminate reentry but also reinitiate either the same or a different reentrant circuit. If the new circuit has a shorter revolution time, this will result in a faster VT.

A Tentative Classification of Acceleration of Clinical VT by PES

From our experimental results in the rabbit heart, three different mechanisms of VT acceleration by PES were identified: 1) induction of double-wave reentry, 2) induction of a functionally determined
Figure 4. Activation maps of acceleration of ventricular tachycardia from a cycle length of 159 to 138 msec by a single stimulus (coupling interval, 100 msec) at the site of the stimulus symbol. Left panel: During the slow tachycardia, impulse propagated counterclockwise around the upper obstacle (thick arrow). Lower obstacle was activated in two directions (thin arrows), and the two waves collided at 136 msec. Right panel: During the accelerated tachycardia, impulse propagated clockwise around the lower obstacle (thick arrow), and the upper obstacle was now activated by two opposite colliding wavefronts (thin arrows). Numbers indicate local activation times in milliseconds. Isochrones are drawn at 10-msec intervals. Circed number on activation maps indicates the site of recording of the electrogram shown at the top. Empty areas in the centers of the maps indicate the two anatomic obstacles created by cryocoagulation. LAD, left anterior descending coronary artery.

Circuit, and 3) a change from one anatomic circuit to another anatomic circuit with a shorter revolution time. Obtaining definite proof for one of these mechanisms of acceleration of VT in the clinical situation is very difficult at the present time and may be possible only by extensive intraoperative mapping. However, from the information obtained in our animal experiments, the following tentative criteria for the different mechanisms of VT acceleration were derived: 1) Induction of double-wave reentry or a change to a different anatomic circuit with the same exit point to the ventricles should result in an accelerated VT with the same QRS complex morphology as the original VT. 2) Induction of a functionally determined circuit or changes in the original anatomic pathway resulting in a different exit point to the ventricles would result in a different QRS morphology of the accelerated VT. 3) In case of double-wave reentry, a high degree of acceleration must occur (cycle length, <70% of the original VT). 4) Because functionally determined circuits in the ventricle are very rapid and have only a short excitable gap,17 the cycle length of the accelerated VT should be close to the duration of the refractory period during VT (cycle length of accelerated VT, <refractory period + 30 msec).

Acceleration of VT with the same QRS morphology and a cycle length longer than 70% of the initial VT almost certainly excludes double-wave reentry as the mechanism of acceleration. In that case, the induction of a smaller anatomic circuit by PES with the same exit point to the ventricles is more likely. The opposite may not be necessarily true because reentry within a faster anatomic pathway with the same exit point to the ventricles may have a cycle length shorter than 70% of the initial VT. On the other hand, acceleration of VT with a different QRS morphology but still a considerable excitable gap (cycle length, >refractory period + 30 msec) makes a functionally determined circuit unlikely and favors induction of reentry within a faster anatomic pathway with a different exit point to the ventricles. Again, the
opposite does not have to be true because a small anatomic pathway may have a very short cycle length (<30 msec longer than the ventricular effective refractory period).

Using the above tentative criteria, we obtained the following classification of acceleration of clinical VT (Table 1):

1) Among the 22 cases of VT acceleration, two VTs had the same QRS morphology and a high degree of acceleration (cycle length of accelerated VT, <70% of the original VT). This suggests double-wave reentry as the mechanism of acceleration (Figure 5).

2) In six cases of VT acceleration, the QRS morphology was the same before and after acceleration, but the cycle length was longer than 70% of the original VT. This suggests induction of reentry within a faster anatomic pathway with the same exit point to the ventricles.

3) In four cases of VT acceleration, there was a change in QRS morphology and a cycle length less than 30 msec longer than the refractory period. This may be in agreement with the properties of a functionally determined circuit.

4) Most accelerated VTs (10 cases) showed a change in QRS morphology and a cycle length more than 30 msec longer than the ventricular refractory period. The most likely explanation in these cases is a change to reentry within a faster anatomic pathway with a different exit point to the ventricles.

**Limitations of the Study**

Our experimental model consisting of one or two rings of healthy, perfused epicardium is clearly an oversimplification of the complex pathophysiological substrate that results after myocardial infarction. Extrapolation of the mechanisms of VT acceleration as found in this experimental model to the clinical setting, therefore, has to be treated with extreme caution.

Although several indirect criteria such as initiation and termination by PES and entrainment and termination by rapid pacing suggest that the clinical VTs were based on a reentrant mechanism, no mapping studies were performed to provide direct evidence of this underlying mechanism. The use of the morphology of the QRS complex before and after acceleration to differentiate the mechanism of acceleration also has important limitations. During intraoperative
epicardial and endocardial mapping of VTs in humans, Langer et al. studied spontaneous changes in VT morphology. They demonstrated that changes in QRS morphology could be due to 1) a change in the endocardial “site of origin” of the tachycardia, or 2) the creation of functional arcs of block resulting in a shift of the area of epicardial breakthrough or predominance of one site of epicardial breakthrough over another. Acceleration of the VT thus can be associated with the development of rate-dependent conduction block outside the reentrant circuit that may alter the pattern of activation of the ventricles without changing the circuit itself.

Likewise, our assumption that acceleration of VT with an excitable gap of more than 30 msec is unlikely to be based on induction of a functional circuit may not hold as a general rule. Although functional circuits usually have an excitable gap shorter than 30 msec in uniform anisotropic ventricular myocardium, the microscopic changes in diseased myocardium may lead to increased nonuniform anisotropy and intramyocardial circuits with a longer excitable gap.

Last, because the excitable gap of accelerated VT could not be measured directly, it was estimated by comparing the VT cycle length after acceleration with the refractory period before acceleration. The rate-dependent shortening of the refractory period thus is not taken into account, leading to some underestimation of the excitable gap. In addition, it is uncertain to what extent measurement of refractory period at the right ventricular apex is representative for the refractory period within the reentrant circuit.

For all these reasons, our attempts to classify acceleration of clinical VT on the basis of the present in vitro observations should be regarded as strictly speculative. Regardless of how uncertain and arbitrary some of the used criteria may be, we believe that a tentative classification of the underlying electrophysiological mechanisms of acceleration may help to explain the electrophysiological substrates of VT in humans.

References

KEY WORDS • ventricular tachycardia • programmed electrical stimulation • reentry • functional circuit
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